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(54) Title: RHODIUM CATALYZED SILAFORMYLATION OF ALDEHYDES AND PRODUCTS OBTAINED THEREFROM

(57) Abstract

Aldehydes substituted with carbon radicals such as alkyl, aromatic, and heterocyclic, can be silaformylated with a silane reagent and carbon monoxide in the presence of rhodium catalyst to produce alpha-silyloxyaldehydes. The alpha-silyloxyaldehydes are useful intermediates in the synthesis of biologically active molecules.

RHODIUM CATALYZED SILAFORMYLATION OF ALDEHYDES AND PRODUCTS OBTAINED THEREFROM

Technical Field. The invention relates to a method for preparing chiral and achiral α-silyloxyaldehydes. More specifically the invention relates to a process for silaformylating aldehydes with a silicon hydride and carbon monoxide in the presence of a rhodium catalyst.

State of the Art. A method for the silaformylation of aldehydes is shown in Murai et al., Angew. Chem. Int. Ed. Engl., 18: 393 and 837 (1979). Three aldehydes, R-CHO; (where R was cyclohexyl, pentyl, and heptyl), were reacted with carbon monoxide (50 Kg/cm^2) and dimethylphenylsilane in the presence of a $Co_2(CO)_8/PPh_3$ catalyst. A benzene solution was used at a temperature of 100°C and a three-fold excess of aldehyde had to be employed. Although this method could produce α-silyloxyaldehydes, the limited substrate scope, high reaction temperatures and pressures, and excess aldehyde limit this method's scope and utility.

It is known that at elevated temperature in the presence of a cobalt catalyst, a silane reagent extensively reacts and thus consumes the desired α-silyloxyaldehyde product. This consumption drastically lowers the yield of the desired α-silyloxyaldehyde based on the starting aldehyde. Although highly desirable, a catalytic synthesis of diastereomerically pure α-silyloxyaldehydes has not been developed.

It would be an improvement in the art to have a catalytic synthesis of α-silyloxyaldehydes useful with a broad range of aldehydes which would operate under reaction conditions wherein the desired product is stable. Such a catalytic process would provide α-silyloxyaldehydes, enhancing these compounds' utility as intermediates in chemical synthesis.

DISCLOSURE OF THE INVENTION

The invention includes a process wherein aldehydes of the formula: R-CHO, (I)

DETAILED DESCRIPTION OF THE INVENTION

The aldehyde used in the process will generally be chosen for its constituent R group. Preferably the R group will be selected from the group of substituted or unsubstituted phenyl, lower (C1 to C4) alkyl, furanyl, pyrrolyl, and thiophenyl.

As used herein, alkyl is preferably a saturated or unsaturated, branched or unbranched hydrocarbon having one to twenty carbon atoms, e.g. methyl, ethyl, isopentyl, and allyl. Alkoxy groups will typically have one to four carbon atoms and include groups such as methoxy and ethoxy.

Aryl, as used herein, is an aromatic hydrocarbon group, preferably having six to ten carbon atoms, such as phenyl or naphthyl.

Aralkyl, as used herein, is an arene group (having both aliphatic and aromatic portions), preferably having seven to thirteen carbon atoms, such as benzyl, ethylbenzyl, n-propylbenzyl, or isobutylbenzyl.

A "substitution" with regard to the various R moieties generally relates to substituting a group such as alkoxy, halogen, hydroxy, nitro, or lower alkyl onto an aromatic ring for a hydrogen that would normally be present. Substitutions can also be made on an alkyl or alkoxy chain.

Halogen, as used herein, generally refers to fluorine, chlorine, bromine or iodine.

A variety of rhodium complexes can be used as a catalyst. Preferred rhodium catalysts for the silaformylation of aldehydes are rhodium cycloöctadiene chloride ($[(COD)RhCl]_2$) or a compound of the formula:

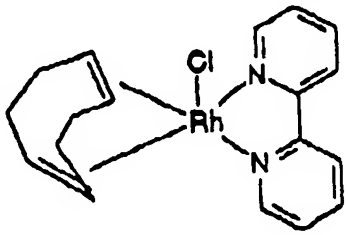
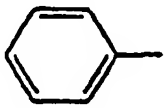
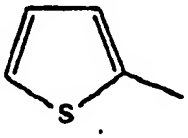
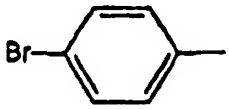
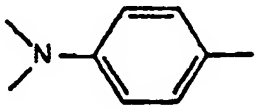
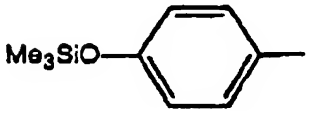
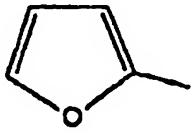
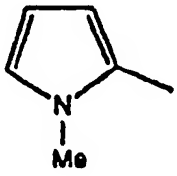
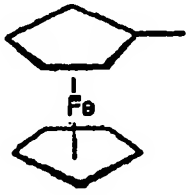


Table I. Summary of Results for the Rhodium Catalyzed Silaformylation of Aldehydes.

Product	R	Yield[b]	Product	R	Yield[b]
3a		74%	3f		72%
3b		84%	3g[c]	$CH_3CH_2CH_2$-	60%
3c		80%	3h[c]	$(CH_3)_2CH$-	75%
3d		50%	3i		90%
3e		60%	3j		88%

The rhodium catalyzed silaformylation is selective for the aldehyde functionality in the presence of an ester. Highly functionalized aromatic compounds have been isolated in 70% yield. Spectral data collected from the crude reaction mixture indicated complete chemoselectivity for the aldehyde group.

The invention is further described by reference to the following illustrative EXAMPLES.

EXAMPLES

Methods. All manipulations of compounds and solvents were carried out by using standard Schlenk techniques. Solvents were degassed and purified by distillation under nitrogen from standard drying agents. Spectroscopic measurements utilized the following instrumentation: ^{1}H NMR, Varian XL 300; ^{13}C NMR, JOEL-270, Varian XL 300 (at 75.4 MHz); Infrared, Perkin Elmer 1750 FT-IR; UV-vis, HP-8452A diode array spectrometer. NMR chemical shifts are reported in δ versus Me_4Si in ^{1}H NMR and assigning the $CDCL_3$ resonance at 77.00 ppm in ^{13}C spectra. The benzaldehyde, 4-bromobenzaldehyde, 4-dimethylaminobenzaldehyde, 1-methyl-2-pyrrolecarboxaldehyde, 2-thiophenecarboxaldehyde, butyraldehyde, isobutyraldehyde, 2-furaldehyde, and ferrocenecarboxaldehyde were purchased from Aldrich Chemical Co. and used as received. Dimethylphenylsilane, triethylsilane, triphenylsilane was purchased from Hüls America, Inc. and used as received. The $[(COS)RhCl]_2$, 4-acetoxybenzaldehyde, and 4-(trimethylsilyloy) benzaldehyde were prepared from literature procedures. Giordano, G.; Crabtree, R.H., Inorg. Synth. 1979, 19, 218; Highet, R.J.; Highet, P.F. J. Org. Chem. 1965, 30, 902; and Cooper, G. J. Org. Chem. 1961, 26, 925. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, Georgia.

Silaformylation Procedure. A round-bottom flask (50mL) was charged with the appropriate aldehyde (1.5 mmol), dimethylphenylsilane (0.20 g, 1.5 mmol), and THF

at 0.1 mm Hg); ^{1}H NMR ($CDCl_3$) δ 9.49 (s, 1 H, C<u>H</u>O), 7.54-7.20 (m, 9 H, Ar CH), 4.92 (s, 1 H, -C<u>H</u>CHO), 0.44, 0.38 (s's, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 198.7 (CHO), 136.1 (Ar C), 135.2 (Ar C), 133.4 (Ar CH), 132.9 (Ar CH), 131.8 (Ar CH), 131.7 (Ar CH), 130.1 (Ar CH), 129.2 (Ar CH), 128.2 (Ar CH), 128.0 (Ar CH), 127.8 (Ar CH), 127.6 (Ar CH), 122.5 (Ar C), 79.4 (-<u>C</u>HCHO), -1.3, -1.4 ($SiCH_3$); IR (CH_2Cl_2) $\nu_{c=o}$ 1731 cm^{-1}. Anal. Calcd for $C_{16}H_{17}O_2BrSi$: C, 55.01; H, 4.91%. Found: C, 54.91; H. 4.95%.

EXAMPLE III

<u>{4-(Me$_2$N)C$_6$H$_4$}CH(OSiMe$_2$Ph)CHO (3c).</u> α-[(phenyldimethylsilyl)oxy]-4-(dimethylamino)benzeneacetaldehyde (80%, bp 130-140°C at 0.1 mm Hg); ^{1}H NMR ($CDCl_3$) δ 9.48 (s, 1 H, C<u>H</u>O), 7.56-7.53 (m, 2 H, Ar CH), 7.40-7.33 (m, 3 H, Ar CH), 7.18-7.16 (m, 2 H, Ar CH), 6.71-6.68 (m, 2 H, Ar CH), 4.91 (s, 1 H, -C<u>H</u>CHO), 2.92 (s, 6 H, N $(CH_3)_2$), 0.40, 0.34, 0.33 (s's, 6 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 198.3 (CHO), 150.4 (Ar C), 136.7 (Ar C), 133.3 (Ar CH), 132.8 (Ar CH), 132.7 (Ar CH), 129.6 (Ar CH), 129.0 (Ar CH), 128.0 (Ar CH), 127.8 (Ar CH), 127.7 (Ar CH), 127.5 (Ar CH), 123.0 (Ar C), 112.3 (Ar CH), 79.8 (-<u>C</u>HCHO), 40.1 ($N(CH_3)_2$), 0.7, -1.2, -1.5 ($SiCH_3$); IR (CH_2Cl_2) $\nu_{c=o}$ 1733 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_2Si$: C, 68.96; H, 7.41%. Found: C, 68.96; H, 7.49%.

EXAMPLE IV

<u>{4-(Me$_3$SiO)C$_6$H$_4$}CH(OSiMe$_2$Ph)CHO (3d).</u> α-[(phenyldimethylsilyl)oxy]-4-[(trimethylsilyl)oxy]benzeneacetaldehyde (50%, bp 130-140°C at 0.1 mm Hg); ^{1} NMR ($CDCl_3$) δ 9.50 (s, 1 H, CHO), 7.54-7.49 (m, 2 H, Ar CH), 7.43-7.29 (m, 3 H, Ar CH), 7.20-7.17 (m, 2 H, Ar CH), 6.86-6.81 (m, 2 H, Ar CH), 4.93 (s, 1 H, -C<u>H</u>CHO), 0.41, 0.35, 0.26 (3 s, 15 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 199.0 (CHO), 155.5 (Ar C), 136.6 (Ar C), 133.5 (Ar CH), 129.9 (Ar CH), 128.9 (Ar C), 128.1 (Ar CH), 127.9 (Ar CH), 127.6 (Ar CH), 120.3 (Ar CH), 79.8 (-<u>C</u>HCHO), 0.2, -1.2, -1.4 ($SiCH_3$); IR

1.81-1.30 (m, 4 H, CH_2's), 0.86 (t, J=7.3 Hz, 3 H, CH_3), 0.43, 0.42, 0.33 (s's, 6 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 203.5 (CHO), 136.8 (Ar C), 133.4 (Ar CH), 133.3 (Ar CH), 132.9 (Ar CH), 129.9 (Ar CH), 129.8 (Ar CH), 129.2 (Ar CH), 127.9 (Ar CH), 127.8 (Ar CH), 127.6 (Ar CH), 78.9 (-CHCHO), 34.3 (-CH_2CHCHO), 17.9 (CH_3CH_2-), 13.8 (CH_3CH_2-) 0.8, -1.4, -1.50 ($SiCH_3$); IR (CH_2Cl_2) $\nu_{c=o}$ 1734 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_2Si$: C, 66.04; H, 8.54%. Found: C, 65.82; H, 8.56%.

EXAMPLE VIII

$(CH_3)_2$CHCH(OSiMe$_2$Ph)CHO (3h). (75%, bp 90 - 100°C at 0.1 mm Hg); ^1H NMR ($CDCl_3$) δ 9.55 (s, 1 H, CHO), 7.64-7.31 (m, 5 H, Ar CH), 3.75 (dd, J=4.9, 1.9 Hz, 1 H, -CHCHO), 2.06-1.99 (m, 1 H, $(CH_3)_2$CH-), 0.93 (d, J=6 Hz, 3 H, $CHCH_3$), 0.91 (d, J=6 Hz, 3 H, $CHCH_3$), 0.41 (s, 6 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 203.9 (CHO), 136.9 (Ar C), 133.4 (Ar CH), 133.3 (Ar CH), 132.9 (Ar CH), 129.8 (Ar CH), 129.6 (Ar CH), 129.2 (Ar CH), 127.8 (Ar CH), 127.6 (Ar CH), 82.0 (-CHCHO), 31.1 ($(CH_3)_2$CH-), 19.2 ($(CH_3)_2$CH-), 18.8 ($(CH_3)_2$CH-), 18.5 ($(CH_3)_2$CH-), 16.8 ($(CH_3)_2$CH-), 14.8 ($(CH_3)_2$CH-), 0.8, -1.46, -1.51, ($SiCH_3$); IR (CH_2Cl_2) $\nu_{c=o}$ 1734 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_2Si$: C, 66.04; H, 8.54%. Found: C, 66.15; H, 8.52%.

EXAMPLE IX

{2-Furyl}CH(OSiMe$_2$Ph)CHO (3i). (90%, bp 90 - 100°C at 0.1 mm Hg); ^1H NMR ($CDCl_3$) δ 9.63 (s, 1 H, CHO), 7.60-7.52 (m, 2 H, Ar CH), 7.43-7.32 (m, 4 H, Ar CH and furyl CH), 6.34-6.32 (m, 1 H, furan CH), 6.28-6.26 (m, 1 H, furyl CH), 5.02 (s, 1 H, CHCHO), 0.40, 0.35, 0.33 (s's, 6 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 196.8 (CHO), 149.3 (furyl C), 143.3 (furyl CH), 136.2 (Ar C), 133.4 (Ar CH), 132.8 (Ar CH), 129.8 (Ar CH), 129.1 (Ar CH), 127.8 (Ar CH), 127.5 (Ar CH), 110.4 (furyl CH), 109.7 (furyl CH), 73.8 (CHCHO), 0.7, -1.5, -1.9 ($SiCH_3$); IR (CH_2Cl_2) $\nu_{c=o}$ 1736 cm^{-1}

EXAMPLE XIII

{4-(Acetoxy)C_6H_4}CH(OSiMe$_2$Ph)CHO (5). α-[(phenyldimethylsilyl)oxy]-4-(acetoxy)benzeneacetaldehyde (70%, purified by flash chromatography through deactivated flourosil); ^{1}H NMR ($CDCl_3$) δ 9.49 (s, 1 H, C<u>H</u>O), 7.53 (dd, <u>J</u>=7.5, 1.8 Hz, 2 H, Ar), 7.40-7.34 (m, 5 H, Ar), 7.09 (D, <u>J</u>=8.4 Hz, 2 H, Ar), 4.98 (d, <u>J</u>=1.8 HZ, 1 H, C<u>H</u>CHO), 2.27 (s, 3H, CH_3), 0.44, 0.39 (s's, 6 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 198.5 (CHO), 169.0 ($O_2\underline{C}CH_3$), 150.6 (Ar C), 133.5 (Ar C), 133.3 (Ar CH), 132.8 (Ar CH), 129.9 (Ar CH), 127.9 (Ar CH), 127.5 (Ar CH), 122.2 (Ar CH), 121.8 (Ar CH), 79.4 (<u>C</u>HCHO), 20.8 (CH_3), -1.4, -1.5 ($SiCH_3$); IR (CH_2Cl_2) $\nu_{c=o}$ 1736 cm^{-1}.

EXAMPLES XIV to XVII

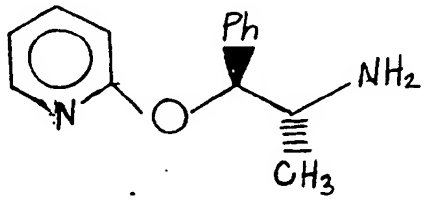
Other monohydridic silane reducing reagents such as Et_3SiH, EtO_3SiH, $MePh_2SiH$ and Ph_3SiH were tested and were found not to be effective reagents for the rhodium(I) catalyzed silaformylation of aldehydes at the mild temperatures employed. Triethylsilane and $MePh_2SiH$ were recovered intact and the triphenylsilane and triethoxysilane decomposed to unidentified products.

References herein to specific Examples or embodiments should not be interpreted as limitations to the invention's scope which is determined by the claims.

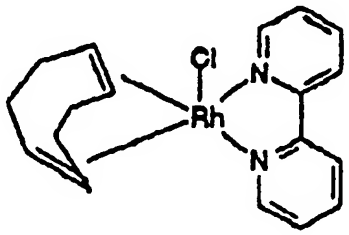
5. The process of claim 1 wherein the rhodium catalyst is a compound of the formula:

$$[L^*RhCl]_2$$

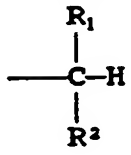
wherein L* is 2,2'-bipyridine, phenanthroline and chiral bidendate nitrogen ligand of the formula:



6. The process of claim 1 wherein said rhodium catalyst is a compound of the formula:



7. The process of claim 1 wherein R is:



and the thus synthesized compound has a specific relative stereochemistry.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00781

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07F 7/08; C07F 7/10; C07D 307/12
US CL :556/427, 436; 548/406; 549/214

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 556/427, 436; 548/406; 549/214

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,124,468(KRAFFT et al.) 23 JUN 1992, see the entire document.	1-7
A	US, A, 4,383,120(YATES) 10 MAY 1983, see the entire document.	1-7
A	US, A, 4,448,980(SOGAH) 15 MAY 1984, see the entire document.	1-7
A	US, A, 4,783,543(SCHULZ et al.) 08 NOV 1988, see the entire document.	1-7
A	US, A, 4,785,126(BRUNO) 15 NOV 1988, see the entire document.	1-7
A	US, A, 2,803,637(SPEIER) 20 AUG 1957, see the entire document.	8-10
A	US, A, 4,424,392(PETTY) 03 JAN 1984, see the entire document.	8-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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